The Office Action

Claims 1-11 are pending in this application. The Examiner notes that the Declaration is defective. Claims 1-11 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 1-11 stand further rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness.

Combined Declaration and Power of Attorney

Applicants note that an executed Combined Declaration and Power of Attorney, including Post Office addresses for each inventor, was filed November 11, 2000, in response to a Notice to File Missing Parts, mailed September 15, 2000. For the Examiner's convenience, a copy of the complete and executed Declaration is enclosed with this reply.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-11 stand rejected under U.S.C. § 112, first paragraph, for lack of enablement. The Examiner asserts that the specification fails to enable a person of ordinary skill in the art to practice the invention as claimed. The Examiner asserts that the specification fails to (i) teach an appropriate method for transferring a recombinant cell into a diseased animal, (ii) provide sufficient guidance to overcome the unpredictability associated with neural tissue transplantation, and (iii) teach a method of expressing a cell fate-inducing gene at a level necessary to produce the desired therapeutic effect. Applicants disagree and address each argument individually.

Applicants' Invention is a Cell Therapy, not a Gene Therapy

First, Applicants respectfully submit that the Examiner has misapprehended the nature of the present invention. The Examiner characterizes the present invention as relating to gene therapy. This is a mischaracterization of the field of the invention. Gene

therapy typically involves prolonged expression of a heterologous gene which replaces a lost or defective protein critical to the disease process. The American Society of Gene Therapy defines the term "gene therapy" as follows:

> The treatment of disease by either replacing damaged or abnormal genes with normal ones, or by providing new genetic instructions to help fight disease, e.g. cancer. Therapeutic genes are transferred into the patient either through a weakened virus, a non-viral vector, or through direct delivery of so-called "naked" DNA. (See, http://www.asgt.org/press_releases/terminology.html)

The present invention is <u>not</u> in the field of gene therapy because, although the transplanted cells are modified by the *ex vivo* insertion of a heterologous gene, the therapeutic benefit of transplantation does not depend on the continued expression of an inserted gene. The present invention neither replaces "damaged or abnormal genes with a normal one," nor "provides new genetic instruction to help fight disease." Rather, according to the invention, totipotent embryonic stem cells (TESCs) are transfected with one or more genes which causes differentiation into a neuronal (or glial) cell type. These cells are then implanted into the nervous system of a patient, where they are allowed to develop as normal neurons (glia), replacing <u>cells</u> lost by the disease process, not a defective gene product. There is no requirement that the cells express the heterologous gene beyond the time required to induce a cell-fate choice. Thus, Applicants' invention can only be characterized as a cell therapy, not a gene therapy. Cell therapies have far more predictable outcomes than do gene therapies.

<u>Cell Transplantation into the Nervous System is Well Known Technique of Art</u>

In support of the non-enablement rejection, the Examiner states (Office Action, page 4, first paragraph):

> The specification fails to teach an appropriate method for transferring a recombinant cell ... [into] a diseased animal, i.e. to produce replacement

neurons at the critical locations.

> The specification fails to provide an enabling disclosure for the method of transplantation because methods of transplantation of neural tissue are not routinely successful and the specification does not offer adequate guidance to enable one skilled in the art to practice the claimed invention to derive a therapeutic benefit in a diseased animal.

To summarize, the Examiner makes two points related to enablement of neural tissue transplantation: (i) methods for neural tissue transplantation are not routine; and (ii) neural tissue transplantation is unpredictable and not routinely successful. Each point will be discussed below.

Surgical Techniques for Neural Tissue Transplantation

Applicants first note that there is no requirement to teach what is already known in the art. The law is clear on this point. The Federal Circuit has repeatedly stated that the law

> permits [Applicant to] resort to material outside of the specification in order to satisfy the enablement portion of the statute because in makes no sense to encumber the specification of a patent with all the knowledge of the past concerning how to make and use the claimed invention. (*Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374 (Fed. Cir. 1999)).

(also see *Spectra-Physics, Inc. v. Coherent, Inc.* 827 F.2d 1524 (Fed. Cir. 1987), stating that "a patent need not teach, and preferably omits, what is well known in the art.")

Applicants submit that methods of cell transplantation into the nervous system for treating neurodegenerative diseases were well known in the art at the time of application filing. Descriptions of human fetal dopaminergic neurons transplanted into the brains of Parkinson's Disease patients were published as early as 1989 (Lindvall *et al.*, Arch. Neurol. 46:615-631; 1989; Ann. Neurol. 31:155-165, 1992; copies enclosed). Specifically, Lindvall describes a stereotaxic technique and implantation apparatus for

grafting cells into the caudate nucleus and putamen of human subjects (Lindvall *et al.*, 1989). Lindvall later describes a refined technique and data demonstrating the long-term (1 year follow up) therapeutic benefit of the implantation procedure (Lindvall *et al.*, 1992). Presently, at least 200 patients have receive tissue transplants using several transplantation techniques, including stereotaxic surgery and open microneurosurgery (Rehncrona, Adv. Tech. Stand. Neurosurg. 23:3-46, 1997; see pages 9-12; copy enclosed). Graft viability has been observed for at least 18 months.

Thus, contrary to the Examiner's assertion, a number of techniques for successfully transplanting tissue into the nervous system were well known in the art at the time of application filing. There is no requirement that Applicants describe such techniques in the specification, just as there would be no requirement that a patent specification describe any standard medical or surgical technique.

Predictability and Expectation of Success of the Claimed Method

The Examiner points out that the specification contains no working examples which demonstrate the therapeutic benefit of the claimed method for treatment of neurodegenerative disorders, and asserts that the transplantation of neural tissue is inherently unpredictable (citing Jackowski *et al.*, Br. J. Neurosurg. 9:303-317, 1995). Applicants traverse these grounds of rejection and note that working examples are not a requirement for enablement and, contrary to the Examiner's assertion, the transplantation of fetal neural tissue is not unpredictable.

First, the Examiner improperly asserts that the claims are unpatentable because no example demonstrating the therapeutic benefit of the claimed method is presented in the specification. Human testing is not required, for enablement purposes, to support claims of an *in vivo* utility. The Federal Circuit has repeatedly stated as much:

> Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings ... Congress has given the

> responsibility to the FDA, not to the [PTO], to determine ... whether drugs are sufficiently safe. (*Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994), affirming *In re Watson*, 517 F.2d 465, 476 (C.C.P.A. 1975) and *In re Sichert*, 566 F.2d 1154, 1160 (C.C.P.A. 1977)).

Accordingly, evidence from sources other than human efficacy trails is acceptable to support enablement. The law is clear on this point. The first paragraph of § 112 "requires nothing more than objective enablement." Where the PTO questions the enablement of a specification:

> It is incumbent upon the Patent Office ... to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. (*In re Marzocchi*, 439 F.2d 220 (C.C.P.A. 1971)).

The Examiner has not provided any evidence or reasons to support the assertion that Applicants' claimed method will not work. Indeed, as is discussed above, the prior art, combined with the teachings in the specification, provides an expectation of success. As reviewed by S. Rehncrona (Adv. Tech. Stand. Neurosurg., 23:3-46, 1997), long term survival of surgically implanted neural tissue has been observed. Specifically, at page 24, Rehncrona states:

> Twelve ... patients referred to ... have undergone flurordopa PET scanning before as well as after transplantation. In 8 of these cases PET demonstrated a marked increase in fluorodopa uptake corresponding to the sites of grafting (citations omitted). The uptake in one patient was modest.

Also noted in Rehncrona are autopsy results from a patient who died 18 months after transplantation, which revealed "well preserved viable grafts with outgrowths of numerous extensions" (paragraph bridging pages 24 and 25).

In asserting that transplantation of neural tissue is unpredictable, the Examiner incorrectly interprets the teachings of Jackowski. Jackowski discusses factors that cause

the CNS to be non-supportive of neuronal proliferation and the axonal regrowth from adult neurons; however, he clearly notes that fetal transplants do not appear to be inhibited by such factors (page 308):

> *Foetal transplants seem exempt.* A clear exception to the non-permissive nature of the adult CNS towards axonal growth, is the target-specific and long-distance fibre outgrowth achieved by some transplanted foetal neurons. Studies by [citations omitted] have shown that donor embryonic hippocampal, or septal neurons from more than one species and also human neuroblasts, when transplanted into an adult mammalian CNS environment can form axons which appear able to grow into and innervate either local or distal target fields within a host animal.

Thus, Jackowski makes clear that fetal cells are not growth restricted in the adult nervous system.

Transplanted cells of the present invention, although not derived directly from a fetus, have many characteristics of fetal cells and are designed to substitute for embryonic stem cells used in traditional transplantation therapy. The specification describes "a method to generate functional lineage-restricted progenitors from embryonic stem cells" (page 3, lines 2-3; emphasis added). The transplanted cells are, therefore, not fully differentiated neurons, and therefore retain the capacity for axonal growth in mature nervous tissue. Thus, contrary to the Examiner's assertion, Jackowski actually shows that transplantation of fetal neural tissue has a predictable outcome and provides the artisan with a expectation of success when practicing the methods of the present invention.

Applicants Enable Cell Fate-inducing Gene Expression

The Examiner asserts:

> At the time the application was filed, the art of administering any type of genetic expression vector, including transfected cells, to an individual so as to

> provide a tangible therapeutic benefit was poorly developed and unpredictable. (Office Action, page 3, first paragraph).

The Examiner cites several references to document and highlight the difficulties associated with gene therapy (Orkin and Motulsky, 1995; Friedmann, 1997; Verma and Somia, 1997). For example, Orkin and Motulsky state that, for the purposes of their review, "genetic material is the putative therapeutic agent" (page 3, last paragraph). Friedmann describes studies in which "transferred genes can be induced to function in the human body, at times for several years" (page 96, middle column). Verma and Somia consider therapy by "putting corrective genetic material into cells" (abstract).

As noted previously, the present invention provides a cell therapy, not a gene therapy. Thus, the present invention is not bound by the uncertainty associated with *in vivo* gene transfer, tissue targeting, and prolonged gene expression. Rather, Applicants' method provides therapy by transplanting cells which are destined to replace those which are lost or damaged by the disease process. The transplanted cells will ultimately become fully differentiated into the selected cell type and fully integrated into the nervous tissue where they will assume the function of the lost cells. There is no requirement for these cells to express a heterologous gene, or even an endogenous gene at levels higher than were present in the naturally occurring cell.

The only genetic manipulation required by the present invention is the transfer and transient expression of a cell fate-inducing gene in cultured TESCs. A plethora of techniques for such manipulation are described in the specification and well known in the art. For example, Applicants disclose a method for inserting Nurr1 into ES cells (Example 2, pages 10-12) and methods for transforming human TESCs (Example 6, pages 17-20, and references therein). Thus, the references and arguments presented by the Examiner are not relevant on the issue of enablement of the present invention.

In sum, Applicants' invention is not a gene therapy, but rather is a cell therapy. Every material teaching required for the successful practice of the claimed cell therapy is

fully described in the specification. Accordingly, a rejection under § 112, first paragraph should be withdrawn.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-11 stand rejected under U.S.C. § 112, second paragraph, for indefiniteness. Specifically, the Examiner asserts that the claim term "cell fate-inducing genes" is indefinite because the term is not defined in the specification. Applicants disagree.

The specification makes clear the metes and bounds of the phrase "cell fate-inducing genes." In summarizing the claimed invention, Applicants state:

> In preferred embodiments of [the claimed] invention, the one or more cell fate inducing genes cause the cells to form [dopaminergic] neurons. In other embodiments of the invention, the [totipotent embryonic stem cells] may, under appropriate conditions, differentiate into neurons, astrocytes, Schwann cells, and/or oligodendrocytes. (page 5, first paragraph).

This passage makes clear that cell fate-inducing genes are genes that cause totipotent embryonic stem cells (TESCs) to differentiate into cell types which normally reside within the nervous system.

Further, in describing methods for transforming the TESCs for the purposes of the invention, Applicants state that:

> TESCs are induced to differentiate into a desired cell type by transfecting the cells with nucleic acid molecules encoding proteins that regulate cell fate decisions (e.g., transcription factors such as Nurr-1, PTX3, Phox2a, AP2, and Shh). (page 18, second paragraph; emphasis added).

Applicants further exemplify the properties of preferred cell fate-inducing genes by pointing out that "Nurr-1 is known to regulate the development of midbrain dopaminergic neurons," "Phox2a is critical for both the development and